Biology of Eating Behavior in Obesity

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Abstract

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Understanding normal and dysfunctional energy regulation and body weight regulation requires neural evaluation of the signals involved in the control of food intake within a meal, as well as signals related to the availability of stored fuels. Work from our laboratory has focused on peripheral and central nervous system studies of behavior and physiology designed to improve our understanding of the role of gut–brain communication in the control of food intake and energy homeostasis. Gastrointestinal administration of nutrients reduces subsequent meal size, suggesting a potent role for peripheral nutrient sensing in the negative feedback control of ingestion. Vagal afferent nerves supply gastrointestinal sites stimulated during food intake, and these nerves are responsive to mechanical and nutrient chemical properties of ingested food. In addition, the presence of nutrients in these gastrointestinal sites stimulates the release of peptides that affect energy intake. These gut peptides also modulate the activity of peripheral gastrointestinal sensory nerves in ways that may contribute to their effects on food intake. In the central nervous system, adiposity hormones and their downstream mediators have been shown to work at both hindbrain and forebrain sites to affect food intake and metabolism. Importantly, recent data has shown that adiposity hormones acting in the brain increase the behavioral and neural potency of feeding inhibitory gastrointestinal stimuli. These data support the suggestion that insensitivity to adiposity hormones in obesity may be characterized by alterations in their ability to modulate the neural processing of food signals important in determining how much food is consumed during a meal.

Key words: gut–brain axis, vagus nerve, visceral afferents, cholecystokinin, leptin

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Introduction

Human eating is a motivated behavior, as well a biological necessity, and is therefore influenced by multiple cognitive, economic, and environmental variables. Understanding the biological basis of eating behavior is critical for understanding the ways in which these extrabiological influences are translated into food intake. Several conceptual and technical advances in behavioral neuroscience, including the discovery of novel bioactive peptides, have promoted a more refined and sophisticated evaluation of the neurobiology of eating. A major conceptual advance is the shift in focus from looking at overall food intake as an outcome of ingestive behavior to the assessment of individual meals. Meals are characterized, in part, by having a discrete beginning and end. For most mammals, including humans, the meal is the behavioral and biological unit of energy intake; therefore, understanding the behavioral neuroscience of eating during meals will be critical to the development of treatments for obesity and related comorbidities.

Consequently, the neurobiological assessment of signals arising from food consumed during a meal is the focus of this discussion. Because meals are distinct temporal events, an analysis of the biological signals that are present and that may contribute to the control of eating behavior is possible. These signals fall into three categories: those involved in the initiation of food intake, those that maintain feeding once a meal has begun, and those mediating meal termination. Meal termination signals may be particularly significant, in that one of the hallmarks of the development and maintenance of obesity is hyperphagia (1). Hyperphagia is characterized by an increased meal size or may also result from increased meal duration. Both features suggest that, in hyperphagia, there is an increase in the exposure to food stimuli that normally provide signals leading to meal termination. Eating behavior in obese individuals may thus be characterized by a reduced sensitivity to the food-stimulated signals that would normally limit energy intake. In this context, it becomes important to identify the neurobiological signals that act to reduce food intake during a meal.

The Gut–Brain Axis

A variety of sensory stimuli occur during a meal and tend to promote food intake, including visual, olfactory, taste,

and other oral stimuli. As eating during a meal proceeds, the presence and accumulation of consumed foods in the stomach and duodenum tract produce a range of mechanical and chemical stimuli, including distension, changes in the gastrointestinal (GI)[1] concentration of nutrients, and alterations in the pH and osmolarity of the GI contents (2). In addition, nutrients absorbed during the digestion of a meal may stimulate sensors in the venous blood supply of the liver (2). Each of these food-elicited stimuli is capable of generating signals in sensory nerves that mediate communication between the GI tract and the central nervous system sites involved in the control of food intake. From a within-meal neural feedback perspective, once a meal has begun, eating may continue until the positive sensory feedback from visual, olfactory, and oral signals is equal and opposite to the negative feedback signals arising from the stimuli provided by ingested food.

The sensory vagus nerve is the major neuroanatomic structure mediating the transmission of the food-elicited negative feedback GI signals critical for determining meal size (2). The gut–brain axis is comprised of the various GI sites handling ingested food, the sensory vagus nerve supplying these sites, and the brain regions receiving the GI vagal sensory signals. The importance of this axis for obesity treatment is supported by the fact that most current surgical antiobesity strategies (gastric banding, gastric bypass, gastric vagal stimulation, and implanted gastric balloons) target GI and vagal components of the axis, and each attempts to increase the potency of food-stimulated negative feedback from the gut to reduce food intake during a meal.

Data from rodent and primate studies that manipulate the degree of GI food stimulation, either by providing meal-related stimuli to the GI tract or by surgically or chemically interrupting gut–brain neural communication, underscore the important role of gut signals in the negative feedback control of meal size. For example, GI infusion of macronutrient solutions (fats, carbohydrates, and proteins) before food access reliably and dose-dependently reduces subsequent meal size. Duodenal lipid infusions have also increased the expression of c-*fos* protein, a marker of neuronal activation, in multiple central nervous system sites that receive GI vagal sensory input, including the nucleus of the solitary tract, area postrema, parabrachial nucleus, hypothalamic paraventricular nucleus, and the central nucleus of the amygdala (3). Conversely, sham feeding, where ingested food passes through a surgical orifice in the stomach without distending the stomach or reaching the small intestine, has lead to dramatic increases in meal size and meal duration, showing both the potent stimulatory role of external sensory factors and the potent inhibitory role of signals arising from GI food stimuli (4).

Interrupting the neural transmission of food-elicited GI signals has also produced significant increases in food intake. Sensory GI vagotomy, which surgically transects all gut sensory vagal fibers, has resulted in increased meal size and meal duration (5). Application of the sensory neurotoxin capsaicin to the vagus nerve or intestinal lumen has also blocked the feeding inhibitory effects of duodenal nutrient infusions (6,7). Blockade of brainstem vagal afferent neurochemical transmission using the pharmacological *N*-methyl-D-aspartate receptor antagonist MK801 has also increased meal size (8). Together, these data support the critical role for the gut–brain axis in the GI negative feedback control of ingestion.

Satiety Peptides Can Alter Meal Size

A second advance in our understanding of the neurobiological basis of eating has come from the finding that food stimuli in the gut evoke the release of feeding modulatory peptides from endocrine cells in the stomach and duodenum. One of these, cholecystokinin (CCK), has been identified as a satiety factor. Exogenous administration of CCK reduces meal size and elicits the complete behavioral sequence of satiety in rodents, consisting of meal termination and a period of grooming followed by sleep. Potent and specific CCK_A receptor antagonists block the satiety effects of GI nutrient infusions and promote eating in sated animals. These data have shown a role for endogenously released CCK in the negative feedback control of ingestion. GI vagal fibers express CCK_A receptors; gastric and duodenal vagal afferent fibers are stimulated by exogenous CCK; and these effects are blocked by CCK_A receptor antagonists (9–12). These data have suggested that GI vagal CCK receptors are important to CCK's satiety effects, an interpretation supported by findings that chemical or surgical sensory vagotomy blocks the satiety effects of exogenous CCK (13).

Another line of evidence supporting a role for CCK in the control of meal size has come from rodent models of genetic CCK_A receptor deficiency. Otsuka Long-Evans Tokushima Fatty mice (OLETF) and CCK_A-receptor knockout mice lack functional CCK_A receptors and have increased meal size (14). OLETF rats are also obese and have an increased susceptibility to the development of type 2 diabetes. OLETF rat hyperphagia has been characterized by a significant increase in the quantity of food eaten, with minimal reduction in meal frequency (15), suggesting that their overeating may be related to their lack of CCK_A receptors. Accordingly, correcting OLETF hyperphagia by limiting the amount of food access to the level of lean controls has prevented the obese, diabetic OLETF phenotype (15). OLETF mice also have a reduced sensitivity to dietary fat, a potent nutrient secretagogue of CCK. As a result, they will

[1] Nonstandard abbreviations: GI, gastrointestinal; CCK, cholecystokinin; OLETF, Otsuka Long-Evans Tokushima Fatty mice; MC4R, melanocortin 4 receptor.

overconsume a high-fat diet relative to lean control rats (16). Together, these results have shown that peripheral gut peptides are important signals in determining meal size, their feeding-inhibiting effects are mediated by the gut–brain axis, and their effects on feeding may contribute to energy balance.

Adiposity Hormones Modulate the Potency of Gut–Brain Signals

A third advance has been the recognition that the neuroendocrine environment and the metabolic status of the organism can both modify the biological significance of food-stimulated GI negative-feedback signals. This has been exemplified by recent work evaluating the role of the adiposity hormone leptin in the control of food intake. Leptin is secreted from white adipose tissue in proportion to adiposity. Leptin has been shown to reach the central nervous system by a saturable transport mechanism, and functional receptors linked to intracellular signaling pathways have been identified at or near hypothalamic and brainstem nodes of the gut–brain axis (17–19). Both central and peripheral administration of exogenous leptin have been shown to reduce food intake by reducing meal size, giving rise to the notion that leptin modulates the potency of sensory food-stimulated negative feedback signals (20,21). Recent findings have confirmed this effect both neurologically and behaviorally. Central leptin at doses that alone have no effect on food intake have increased the ability of gastric nutrient loads and CCK to reduce meal size (22,23). The combination of peripheral meal-related stimuli and central leptin have also increased the number of neurons expressing c-*fos* protein (a marker of neuronal activation) at both brainstem and hypothalamic areas of the gut–brain axis (23). These data have suggested that these feeding behavioral effects are mediated by these neuronal populations. Recent neurophysiologic data have supported the idea that central leptin modulates the neural potency of GI food-related feedback signals at the level of the individual neuron as well. Central leptin administration has increased the neurophysiologic response to gastric loads in single units in the brainstem nucleus of the solitary tract (24). The ability of leptin to modulate the controls of meal size has also begun to be pursued from a transgenic rescue strategy. Obese diabetic *db/db* mice, which lack leptin receptors, overeat, have increased meal size, and have shown no reduction in food intake after central leptin injection. Transgenic neuron-specific replacement of leptin receptors in *db/db* mice results in animals whose food intake and meal size are comparable with lean wild-type C57B6J controls, are not obese or diabetic, and have reduced their food intake in response to central leptin administration (25,26). Together, these findings have supported the ideas that the metabolic and neuroendocrine context (determined, in part, by leptin levels in obesity) is important in the neural evaluation of meal-stimulated negative feedback signals, and the central nervous system integrates adiposity signals with gut feedback signals in determining meal size.

Central peptide signaling systems downstream from leptin have begun to be examined in this manner. Research into the melanocortin 4 receptor (MC4R) signaling system (27) and agouti-related protein, an MC4R antagonist, has implicated these systems in some eating disorders. Deletions of MC4R in rodent models have resulted in hyperphagia and obesity, and MC4R agonists have reduced food intake in rodents by reducing meal size, not meal frequency (28,29). In contrast, central administration of agouti-related protein has significantly increased food intake in rats and mice, and this increase has been completely accounted for by a significant increase in meal size, with no change in meal number (unpublished observations).

Summary and Future Prospects

Meals are the biological units of eating behavior in humans, and the gut–brain axis is a critical neural network in the control of energy intake and meal size. Food-stimulated gut peptides act on this axis to produce and modulate negative feedback signals that limit energy intake during meals. Adiposity hormones and hypothalamic neuropeptides also are able to affect food intake by altering meal size and seem to do so by modulating the potency of food-stimulated GI sensory signals. These neurobiological mechanisms have primarily been shown in normal weight rodent models, and many await verification in humans. In addition, their function in the development or maintenance of obesity is likely altered in ways that are important but remain unknown.

Human neuroimaging studies have begun to focus on the pattern of brain activation produced by food. Results of these imaging studies in normal weight individuals have suggested that certain regions of the brain are responsive to multiple sensory and GI food stimuli (30). Although primarily phenomenological, results from these studies have the potential to provide neuroanatomic targets for subsequent neurobiological investigation in animal models. Given the wide range of powerful molecular/genetic, physiological, behavioral, and neuroimaging tools currently available, our understanding of the neurobiological basis of eating in obesity will profit from an approach that incorporates both animal and human research programs.

Question and Answer Period

Dr. Roth. I was fascinated by the various regulations of meal size and intake. Could you tell us how you think that involves slow and fast eaters in humans? I think that's one of the questions that puzzles us.

Dr. Schwartz. Eating style may be a very important factor in terms of the availability and processing of GI satiety signals. Mike Devlin's work (31) on disordered eating, binging, and altered satiety signals has shown a significant effect of eating style. CCK release, for example, is very different in binging individuals, suggesting that it is not as efficient as a satiety signal. It remains unclear whether a primary deficit in eating style promotes a change in the way GI satiety signals become available or vice versa. How the central nervous system deals with these signals in terms of everyday eating behavior is probably a plastic process and contributes to both the etiology and maintenance of a feeding disorder.

Audience Member. You talked about the mouse that persisted in attempting to obtain food even when food was not present. If that was a human, would you talk about slow learning or perseveration or what's the difference there?

Dr. Schwartz. The tests that I showed were ones where the animals were trained to have to increase the amount of work to receive food reinforcement. With that experience, they will perform a great deal of work when no food is available. From a clinical perspective, it's not clear how that would represent perseveration. Food-seeking is likely going to be opportunistic and occupy larger amounts of time in individuals that are prone to eat larger meals.

Audience Member. Or perhaps be more difficult to change because the learning process, even in the absence of strong positive feedback, might be hard to eliminate.

Dr. Schwartz. That's an empirical question. It's not unreasonable to imagine neuronal plasticity changes that maintain a large degree of food-seeking behavior even when the reward isn't available.

Dr. Roth. Has anyone looked at the effect of success in obesity treatment based on meal frequency or meal size?

Dr. Schwartz. Not to my knowledge. There are anecdotal reports that suggest that eating more slowly is effective by maximizing the chance that the person will be sensitive to signals that terminate intake.

Dr. Segal-Isaacson. Basically, the question is how CCK and other neural impulses and hormones regulate appetite and food consumption in a normal situation. We currently have a kitten who is quickly becoming a cat who is outeating, both in terms of meal size and meal frequency, all of the other cats in our family. What is controlling, in terms of signaling, his hunger impulses: this cat is not fat, he is very thin, very active, but eating at a ferocious rate. Similarly, in a human, if you do a tremendous amount of exercise, a marathon, a very long bicycle trip, you're not very hungry the first day, but over a few days you find that you're hungrier more often. What controls all of that?

Dr. Schwartz. The biological basis of meal initiation, which is part of the gist of your question, is largely unknown. Clearly there are a variety of social, cognitive, and environmental factors that drive our behavior. The possibility that blood glucose trajectory is important in determining meal onset has been suggested (32). In addition, studies of ghrelin, a GI peptide whose plasma levels increase with deprivation and drop after a meal, have been suggested as signals for meal initiation. What is clear is that, when you eat, plasma ghrelin levels are reduced (33). What is not clear is that the level of ghrelin at any particular time is important for initiating a meal. I think more detailed neuroendocrine profiling before, during, and after meals will be necessary to make stronger conjectures about the role of gut–brain peptides in meal initiation.

Dr. Roth. If I understood you correctly, a lipid load in the duodenum reduces subsequent meal size.

Dr. Schwartz. Correct.

Dr. Roth. So, I don't mean to be flippant, but it strikes me that if you started every meal with a shrimp cocktail and a handful of macadamia nuts, perfect Atkins strategy, and waited 20 minutes to load your duodenum, you would reduce subsequent meal size and enhance the efficacy of the diet. These are Atkins maneuvers that would be perfectly reasonable, and now you make a scientific rationale for reducing subsequent meal size.

Dr. Schwartz. In rodent models, protein and fat infusions in the duodenum are much more efficacious in reducing subsequent food intake than equally caloric loads of carbohydrate. They are also particularly good secretogogues of CCK. So mechanistically speaking, it's not unreasonable to imagine that preconsumption, if you will, increases the availability of nutrient secretogogues of the satiety peptides that are mechanistically important in regulating the subsequent meal size.

Dr. Feinman. Do carbohydrates, more particularly sucrose, have an effect? In particular, would vagal stimulation be repressed by the presence of sucrose?

Dr. Schwartz. An individual macronutrient may have different behavioral and neural effects at different gut–brain sites. At an oral site, it has been shown that sucrose can promote the release of dopamine in the forebrain nucleus acumens, part of the neuranatomic basis of reward. Duodenal infusions of carbohydrate solutions can promote increases in vagal afferent activity, yet these infusions also reduce subsequent meal size.

Dr. Roth. Let me just make a couple of comments along the way. The question that was raised from the audience that was very good and that I found fascinating was not so much about the meal-to-meal regulation of caloric intake, but the long-term regulation of body weight. You watch people and they'll yo-yo up and down a few pounds but at the beginning and end of the year they're really pretty much the same weight. The error is $<1\%$, despite all those components that we know about. The question is how do you determine your set-point, or the weight that you come back to. There are so many components and the error rate is so small, despite the enormous number of players.

Dr. Schwartz. I think that the idea of a set-point really reflects the outcome of a variety of effectors. I doubt it will be the case that individual peptides will affect food intake alone, energy expenditure alone, or nutrient partitioning alone. Rather, it seems more likely that individual peptides will have effects on more than one of these arms of the equation. More careful study of how each gut–brain peptide affects each of these measures is required.

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